Computational Studies on the Nucleophilic Destruction of the Nerve Agent VX

Kelly A. Daniel, Laura A. Kopff, Eric V. Patterson*
Truman State University Division of Science, 100 E. Normal, Kirksville, Mo 63501

Abstract
O-ethyl S-[2-(disopropylamino)ethyl] methylphosphonothioate (VX), is a nonvolatile liquid chemical warfare agent. VX is a potent irreversible acetylcholinesterase inhibitor; exposure to a lethal dose of VX results in convulsions, loss of muscle control and death through asphyxiation within 15 minutes. Neutralization of this deadly nerve agent requires cleavage of the P-S bond. Hydrolysis in alkaline solution results in both P-S (87%) and P-O (13%) bond cleavage, with the product from P-O bond cleavage remaining highly toxic. The hydroperoxidolysis of VX results in exclusive P-S bond cleavage. The potential energy surface for the reaction of hydroxide and hydroperoxide with VX has been computed at the MP2/6-31+G(d)//MPW1K/MIDI! level of theory, with corrections added for thermodynamic and solvation effects. The results clarify the mechanism and suggest an unusual oxygen migration between the phosphorous and sulfur atoms during hydroperoxidolysis.

Theoretical Calculations

- Stationary point geometries were calculated using MPW1K/MIDI!
- Single point energies were calculated using MP2/6-31+G(d)
- Corrections were made for aqueous solvation using IEF-PCM, HF/6-31+G(d)

Results

Alkaline Hydrolysis:
- Three major pathways:
  - Attack opposite thiolate group
  - Attack opposite ethoxide group with side chain stabilization
  - Attack opposite ethoxide group with pseudorotation resulting in P-S cleavage

Results:
- 15:1 ratio between transition state for attack opposite ethoxide and attack opposite thiolate group
- Pseudorotation versus P-O cleavage has a ratio of 188:1
- Taking into account +/- 1 kcal/mol errors in energy calculations:
  - Pseudorotation versus P-O cleavage has a ratio of 149:1

Hydroperoxidolysis:
- Four major pathways:
  - Attack opposite thiolate group
  - Attack opposite ethoxide with oxidation resulting in P-S cleavage
  - Attack opposite ethoxide with pseudorotation resulting in P-S cleavage
  - Attack opposite ethoxide group resulting in P-O cleavage

Results:
- 94:1 ratio between P-O cleavage and P-S cleavage products expected from initial attack transition state
- Attack opposite ethoxide results in pseudorotation and oxidation yielding exclusive P-S cleavage

Conclusion:
- Alkaline hydrolysis results in competing reactions with a 6:1 ratio, as expected from experimental and previous computational results.
- Hydroperoxidolysis results in exclusive P-S cleavage as predicted by model system.

Acknowledgements and References:
Truman State University
Department of Chemistry
Vice President for Academic Affairs